Successful Surgical Treatment of an Infected Right Coronary Artery Aneurysm-to-Right Ventricle Fistula after Sirolimus-eluting Stent Implantation

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Abstract

The development of infected coronary aneurysmal fistula following stenting seems exceedingly rare. A sirolimus-eluting stent (SES) was implanted in a 70-year-old male patient for acute coronary syndrome. His fever persisted despite treatment with adapted antibiotics. Coronary angiography and 16-multidetector row computed tomography demonstrated the huge right coronary aneurysm forming a fistula to the right ventricle. The aneurysm was excised by surgical treatment. Histopathological examination of the resected mass revealed leucocyte infiltration at the stent site, which led to the diagnosis of mycotic aneurysm. SESs may play a potential role in locally blunting the innate response to bacterial agents.

Key words: sirolimus-eluting stent, infected aneurysm, fistula, local immunosuppression

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Introduction

To date, coronary stenting for acute coronary syndrome has been widely used (1, 2). Complications following stent implantation include thrombosis, rupture, sepsis and infected coronary aneurysm (1, 2). Among them, infected coronary aneurysm causes fatal outcome. In addition to contamination at the time of stent delivery, there are other mechanisms how stents can become infected, including transient bacteremia from skin flora via access-site hematomas, pseudoaneurysms, delayed bleeding, prolonged arterial sheath insertion, and several procedures performed from the same access site over a short time period (1). However, prophylactic antibiotic administration does not appear to be conducted routinely prior to coronary angioplasty stenting, because the incident rate of stent infections was reported to be less than one in 10,000 cases (1-3). Recently, coronary artery aneurysm formation is considered as one of complications after the use of sirolimus-eluting stent (SES), which markedly reduces the restenosis rate after coronary angioplasty (3, 4). Development of mycotic aneurysms after stenting SES has

only been reported in two cases (5, 6). Furthermore, the incidence of infected aneurysmal fistula formation after stenting SES has not been presented. Here, we report a case of recurrent unknown fever who developed infected coronary aneurysm with fistula at the site of stent implantation, which was diagnosed by coronary angiography and 16-multidetector row computed tomography (MDCT).

Case Report

A 70-year-old man was admitted to our hospital with sustained angina. His past medical histories were hypertension, diabetic mellitus, mild renal dysfunction (serum creatinine levels was 1.6 mg/dL) and old cerebral infarction. Electrocardiogram (ECG) on admission revealed predominant ST segment changes in II, III, and aVF leads. Using the right trans-radial approach method, emergent coronary angiography demonstrated a 99%-delayed tight stenosis in the proximal right coronary artery (RCA) (Fig. 1A), and significant stenosis in the proximal left anterior descending artery (LAD) (Fig. 2A) and the middle circumflex artery (LCX) (Fig. 2B). The patient was diagnosed with the culprit lesions

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Figure 1. Right coronary artery angiogram performed during the initial procedure. Preangioplasty (left anterior oblique (LAO) view): the right coronary artery (RCA) was affected with severe stenosis in the proximal site (arrow) (A). The RCA was opened and a sirolimus-eluting stent (SES) was inserted (B). Satisfactory angiographic results were obtained with a smooth luminal outline. No contrast extravasation outside the vessel wall was noted on the image.

Figure 2. Left coronary artery (LCA) angiograms performed during the initial procedure. Preangioplasty (cranial and caudal views): significant stenosis (arrow) was also exhibited in the left anterior descending artery (LAD) (A) and the middle circumflex artery (LCX) (B). Both LAD and LCX were opened and each limus-eluting stent (SES) was inserted with a good immediate angiographic result (C, D) after the appearance of lethal arrhythmias.

of proximal RCA. It was difficult to hook RCA with various guide catheters because of a tortuous innominate artery. The lesion was barely crossed with an internal mammary artery catheter and universal guidewire by using the balloon anchor technique (7). The procedure, however, was cumbersome and prolonged because of vessel curvature and poor guiding catheter back up. Two sirolimus-eluting stents (SES, Cypher® Cordis Johnson & Johnson, Japan) (2.5×28 and 2.5×23 mm) were deployed in the stenosed vessel (Fig. 1B) at 16 atm for 30 seconds. Incomplete dilated RCA at the site of stent was postdilated with a 2.5 mm balloon. The volume of contrast used in this procedure was 189 mL. Although the catheter of intravascular ultrasound (IVUS) did not finally cross the RCA lesions because of severe calcification of RCA tortuously, the end result was good without use of oversized balloon size, high-pressure inflation of the balloon, coronary dissection and contrast extravasation outside the vessel wall. Satisfactory angiographic results were obtained with a smooth luminal outline, and then the arterial sheath was removed.

The day after the procedure, the patient had fever, chills, malaise and no suppuration on the access site. Blood cultures yielded repeatedly *Staphylococcus aureus* (*S. aureus*) and echography revealed neither valvular nor myocardial abnormalities. Urinalysis was negative and no line sepsis was found. Despite exhaustive screening for a potential source of the infection (including whole computed tomographic scan, transesophageal echocardiography, gastric endoscopic examination and gallium scintigraphy), no infectious focus was detected. The interventions for the residual left coronary artery (LCAs) lesions were necessary to perform. Intravenous adapted antibiotics was administrated, however, the patient's condition remained poor. A watchful waiting strategy, with aggressive intravenous antibiotic treatment, was selected because of progressive inflammatory signs and relapse of renal dysfunction (serum creatinine levels was 2.0 mg/dL). Three weeks later he started to have fever, convulsion and syncope attack, accompanied by the torsades de pointes on ECG monitor. The causes were considered to be due to trouble of LCAs. Percutaneous transluminal coronary angioplasty of the LCAs was attempted. Two SESs (3.0×28 and 3.0×28 mm) were successfully implanted to completely cover the target LAD stenosis at 16 atm and post-dilate with 3.5 mm balloon (Fig. 2C). A SES (3.0×33 mm) was inserted to the target LCX stenosis at 16 atm (Fig. 2D). The volume of contrast used was a minimum of 15 mL with IVUS. The regions were suspected to have occlusion or severe stenosis of RCA because final angiography demonstrated delayed retrograde filling images by collaterals from LCA to distal part of RCA. The patient had fever and renal dysfunction. Myocardium controlled by RCA was infarcted and it was a concern that the increasing use of contrast volume would aggravate renal dysfunction due to the difficulty of percutaneous transluminal coronary angioplasty for tortuous RCA. The patient was subjected to coronary angioplasty to the LCAs alone. The postprocedural course was uneventful, and the in-

flammatory signs were improved by the treatment with adapted antibiotics. The patient was transferred to a different hospital for the rehabilitation.

Two months later, the recurrence of high fever with eosinophilia led to a readmission to our hospital with the relapse of renal dysfunction (serum creatinine level was 3.7 mg/dL) and there was ST-segment depression in I, aVL, II, III and aVF leads on ECG. Clinical examination did not reveal any findings which suggested the cause of fever. There were no vegetations. The patient underwent a coronary angiogram as he had developed ischemia. The LCAs were unchanged compared with the previous final results (Fig. 3A), while the RCA was completely occluded at the stent portion (Fig. 3B-a), near the aneurismal dilatation (Fig. 3B-b) with the evidence of contrast spilling into the right ventricular chamber with rapid clearance (Fig. 3B-c). The volume of contrast used was 23 mL. A Swan-Ganz catheter was subsequently inserted and right heart catheterization was performed for the oxygen saturation run. No significant step-up in oxygen saturation data was observed between the venous samples obtained from the vena cava and right ventricular, thereby concluding that the shunt fraction between the pulmonary and systemic (Qp/Qs) circulation was hemodynamically insignificant and less than 1.11 ratio at that particular time point. The pressure of the pulmonary artery, pulmonary artery wedge, right atrium, inferior vena cava and superior vena cava indicated 46/16 (30), 17, 49/6 (13), 10, 9 and 12 mmHg, respectively. The 16-multidetector row computed tomography (MDCT) scan demonstrated the occlusion of proximal RCA (Fig. 4A-a, Fig. 4B-a and -b), and a large aneurysm (50×30 mm in size, Fig. 4A-b, Fig. 4B-a and 4C) forming a fistula (10 mm in size) between the aneurysm and right ventricle (Fig. 4A-c). The volume of contrast used on MDCT was 85 mL. This coronary aneurismal fistulation was suggestive of an infectious focus. No revascularization was performed with coronary intervention. The decision was made to continue medical management because of the patient's complicated conditions. The fever persisted despite intravenous adapted antibiotic treatment. Finally, an elective operation was conducted. The surgical treatment consisted of stent removal and excision of the right coronary artery aneurysm without coronary artery bypass grafting. The right ventricular wall was reconstructed (Fig. 5A, 5B). Histopathological examination of the resected aneurismal wall revealed an extensive inflammatory reaction in the inner layer of the arterial wall, with destruction of the media and the formation of some microabscess [Fig. 5C (original magnification ×20), 5D (original magnification ×200)]. Bacterial cultures of the resected stent showed no growth. The patient started to respond favorably to the antibiotics (Fig. 6). Infection parameters were normalized and the patient could be transferred to a different hospital for rehabilitation. There has been no recurrence of fever or angina in the past 16 months.

Figure 3. A, A coronary angiogram showed no change of left coronary arteries (LCAs) compared with the previous procedure. B, Angiography of the right coronary artery (RCA) demonstrated occlusion of proximal stent site (solid arrow), an entry point to aneurysm (dotted arrow) (a), and the saccular aneurysm (dotted arrow) in the area of proximal stents and its coronary artery fistula originating from the RCA stents (b), with contrast spillage into the right ventricular chamber (c) through the fistula (solid arrow). Rapid clearance of contrast was observed, with none in the pericardial space.

Discussion

The advancement of coronary intervention for coronary artery disease has provided cardiologists with a wider range of treatment (8). Development of intracoronary stents has facilitated a much less invasive therapy than open-heart surgery (9). Infection specificity, related to the use of intracoronary stents, is exceedingly rare. The reported infected coronary aneurysms at the stent sites are summarized in Table 1 (5, 6, 10-16)). Bacterial cultures of blood in the present case repeatedly grew *S. aureus* (Fig. 6). Of the 11 reports in the literature, including the present case, the potentially responsible bacteremia was either *S. aureus* (n=8) or *Pseudomonas aeruginosa* (n=2) (Table 1). The mechanism of sepsis remains unclear, because there had been no evidence of local access site infection following intervention. Mortality was fairly high, with death occurring in four of the eleven patients (Table 1). Myles et al reported a case managed solely with medical therapy (3). Five of seven patients treated surgically lived (Table 1). Therefore, if an infected coronary aneurysm is detected, prompt surgical excision of the stent and debridement of infected tissues is recommended to minimize the risk of rupture, cardiac tamponade and sudden death (10-13). The present case was quite rare in that the mycotic stented aneurysm formed a fistula to the cardiac chamber. This case is the first report of successful surgical treatment of an infected aneurysmal fistula after SES implantation.

Why did infection develop in the present case at the site of sirolimus-eluting stenting? Sirolimus, belonging to rapamycin, has been used for systemic therapy in renal transplant patients (17). Sirolimus is capable of inhibiting not only elastic recoil and arterial remodeling caused by vascular injury, but also neointimal hyperplasia after angioplasty (9). The drug-eluting stent era was ushered in with the first published human study by Sousa et al in 2001, showing nearly complete abolition of neointimal hyperplasia by use of SES (18). In Japan, the use of SESs has been approved since 2004. Despite the dramatic capacity of SES to reduce the restenosis rate, SES-related local problems have been reported (9). First, the requirement of a prolonged dual antiplatelet regimen to avoid the risk of SES thrombosis is widely accepted (19). Second, the occurrence of acquired late malapposition in some patients suggests a continuous interaction of SES with the vessel wall promoting vessel remodeling. It has been recently reported that the implantation of a SES may cause late formation of coronary artery aneurysm (4). SES having an antiproliferative action may be responsible for the delayed and inappropriate healing, which likely leads to weakening of the arterial wall and delayed aneurysm formation (20). Third, local hypersensitivity has been documented in some patients suffering complications after SES implantation (21, 22). Virmani et al have shown that aneurysmal dilatation of stented arterial segments is due to a severe localized hypersensitivity consisting predominantly of T lymphocytes and eosinophils (21), which is caused by the metallic stent, polymer, or sirolimus (21-23).

Figure 4. The 16-row multislice computed tomographic scan disclosed huge right coronary artery (RCA) aneurysm and draining image into right ventricular chamber via fistula. The large aneurysm was located between the proximal and distal areas of the stented region. The aneurysm did not connect to the stented lumen distal to the occlusion. The maximum intensity projection in longitudinal sections (A-a, b, c) and cross sections (B-a, b), and volume rendering (C) images of the markedly dilated RCA is indicated. The fistula foramen measured 10×10 mm in diameter (A-c). Ao; ascending aorta, RV; right ventricle, LMCA; left main coronary artery, LAD; left anterior ascending artery.

Figure 5. Intraoperative image of the coronary aneurysm before (A), and after excision and excised stent (B-b) and infected coronary aneurysm (B-a). Pathology of the false aneurysm after surgical excision (C). The aneurysm without neck measured 50×30 mm in size and had a red appearance like normal vascular color. Its histopathologic examination demonstrated marked inflammatory reaction consisting of leucocytes within media (hematoxylin and eosin stain; original magnification ×20, ×200) without eosinophilic reaction.

We doubt that in the present case it was due to a similar aneurismal formation (Fig. 3A) and there was no infiltration of eosinophilia in focus (Fig. 5C, 5D). Finally, could the ef-

Figure 6. Clinical course, and white blood cell counts (WBC, filled circle), eosinophil counts (Eos, filled square), and C-reactive protein (CRP, filled triangle) levels in blood. OPE: operation, *S. aureus*; *Staphylococcus aureus* (open arrow). CAG: coronary angiogram, PCI: percutaneous coronary intervention. Each antibiotic, CTM; cefotiam, LVFX; levofloxacin, VCM; vancomycin, CTRX; ceftriaxone, CZOP; ceftazopran, IMP/CS; imipenem/ cilastatin, PIPC; piperacillin.

Table 1. Infected Stented Coronary Aneurysm

Case	Vessel	Stent	Fistula	Organism	Days	Max size	Ope	Outcome	Reference
66yo F	RCA	PS	—	<i>S. aureus</i>	30	32	+	Dead	1993 Gunther
49yo M	LAD	PS	—	<i>P. aeruginosa</i>	60	—	+	Dead	1996 Leroy
65yo M	RCA	PS	RA	unknown	90	—	+	Alive	1996 Karim
38yo M	LCX	PS	—	<i>P. aeruginosa</i>	10	16	+	Alive	1997 Bouchart
54yo M	LAD	MS	—	<i>S. aureus</i>	3	17	—	Dead	1999 Grewe
67yo M	LCX	PS	—	<i>S. aureus</i>	120	—	—	Alive	2000 Rensing
55yo M	LAD	P	—	<i>S. aureus</i>	90	15	+	Alive	2005 Marcu
47yo M	RCA	S	—	<i>S. aureus</i>	2	—	—	Dead	2005 Alfonso
56yo M	LAD	S	—	<i>S. aureus</i>	30	28	+	Alive	2005 Singh
70yo M	RCA	S	RV	<i>S. aureus</i>	120	50	+	Alive	2005 our case

PS: Palmaz-Schatz stent, MS: micro stent, P: paclitaxel eluting stent, S: sirolimus eluting stent. *S.*: *Staphylococcus*, *P.*: *Pseudomonas*, F: female, M: male, RCA: right coronary artery, LAD: left anterior descending artery, LCX: left circumflex artery, RA: right atrium, RV: right ventricle, Days: onset of aneurysm, Max size: max diameter of aneurysm, Ope: surgical operation

fects of sirolimus on the vessel wall at the site of SES implantation contribute to the development of infection? If infection does occur locally in the procedural period, it is likely that sirolimus might contribute to the development of aneurysms by suppression of the healing process and local immune response after artery injury. The cases of Alfonso et al (5) and Singh et al (6) developed the mycotic aneurysms at the site of SES implantation. Sirolimus has well-known effects on suppression of the immune response. The potential role of SES in locally blunting the innate response to

bacterial agents may be considered. The formation of mycotic aneurismal fistula in the present case may be partly accounted for by this mechanism.

In conclusion, the objective signs of infection (unexplained fever, late or relapsing bacteremia) following coronary stenting should motivate cardiologists to perform non-invasive diagnosis, MDCT, to determine coronary infective aneurysm either with or without fistula.

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